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# EFFECT OF Y90 ON THE NERVOUS SYSTEM IN CONNECTION WITH THE POSSIBILITY OF USING IT IN EXPERIMENT AND IN THE NEUROSURGICAL CLINIC

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By means of subsequent tempering at 800° to 850° temperature, filaments of ceramic yttrium of 0.3 -- 0.5 mm in diameter and 1 -- 3 mm in length were obtained. The mixture of $Sr^{90}$ in these preparations did not exceed $5:10^{-4}$ percent (V. I. Levin). The metallic preparation Y90 was obtained by irradiation of $Y^{89}$ in a reactor with a stream of slow neutrons of $0.8.10^{13}$ micron H per square cm per second. The metallic yttrium was used in the form of cylindrical rods: diameter 0.3 -- 1.3 mm, length 1.5 -- 3 mm. Both varieties of the preparation are virtually insoluble in the tissue liquid. The range of activities of Y90 was within the limits of 12 micron/c to 1.13 cm.

The introduction of Y90 in the form of a ceramic or metallic rod into the rabbit's hypophysis was carried out by means of a regular injection needle with a diameter which corresponded to the size of the rod. The approach to the hypophysis was effected through the mouth by opening it maximally with the aid of a mouth-dilator. The needle containing the preparation was inserted at the borderline between the upper and posterior walls of the oral part of the pharynx along the median line. The needle was then moved to a depth of 9 - 10 mm and the preparation was pushed out with a stylet. To insert the tip of the needle correctly into the fossa of the sella turcica, it is essential that the distance from the site of the introduction of the needle to the upper anterior incisers equalled 51 mm, and the perpendicular line carried down from the upper incisors to the needle equalled three mm. Immediately following the operation, there was a brief secretion of blood observed. The position of the yttrium rod was checked roentgenographically in two projections.

All animals were subjected to a systematic clinical examination. Measurements of their body temperature; the electrocardiogram recording, the number of respiratory movements and the size of the pupils were all evaluated, while the neurological symptoms and the permeability of vessels of the ciliary tract were studied. To evaluate the functional state of the adjacent centers of the subthalamic region, investigations were made of the reaction of the pupils, respiration, heart (according to ECG data), and the reaction of the cutaneous vessels of the cochlea to the electric stimulation of the hypothalamus by means of implanted electrodes.

As a result of the introduction of Y90 into the hypophysis, there developed in the rabbits a complicated symptomocomplex the decoding of which required a thorough analysis.

A number of the symptoms observed can be explained by

the direct stimulation of the incretory tissue of the hypophysis which resulted in an enhanced discharge of hormones. These phenomena include an increased permeability of the vessels of the ciliary tract during the early stages following the insertion of the needle; not always discernible but clearly pronounced in cases where it was detected.

This fact can be demonstrated in Fig. 1 where curves are presented which characterize the rate of exit of the intravenously injected fluorescein into the anterior eye chamber of the rabbit in norm and within three hours, following the introduction of Y90 of 570 micron/c activity into the hypophysis.

During the early stages (the first three or four days) there was observed a considerable increase in the size and duration of the vascular reaction which originated in response to the electrical stimulation of the hypothalamic region. Fig. 2 shows the sizes and duration of vascular reactions in rabbits which had received Y90 of 250 and 570 micron/c activity, before and after the introduction of Y90. These changes occurred because of the stimulation of the hypophysis and the enhancement of the incretory component of the reaction. Subsequently, a normalization of the permeability of the ciliary tract vessels was observed as well as the intensity of cutaneous vascular reactions. This circumstance confirms the fact that the described phenomena must be regarded as a manifestation of a true stimulation of the glandular tissue of the hypophysis.

Besides these phenomena, there was observed, during the early stages following the introduction of the isotope, a number of transitory symptoms varying in intensity and duration.

Among them were: a) anisocoria; b) impairment of thermoregulation which expressed itself in a rise (up to 40°C), or fall (to 36 - 34.6°) of the body temperature during the first hours -- and sometimes within 24 hours -- following the operation; c) slowing up of respiration, not infrequently the appearance of arhythmic respiration; d) tendency toward retardation of the cardiac rhythm; e) higher T wave on the ECG, acquiring at times a steeple-shaped form.

Following the phase of apparent normalization, when the described phenomena ceased to manifest themselves, a number of phenomena can be elicited most likely, connected, not with the stimulation of the hypophysis but with the inhibition of its functions. Thus, in some cases, a tendency was noted toward the reduction of vascular permeability (on the second, fourth, and seventh day following the effect of

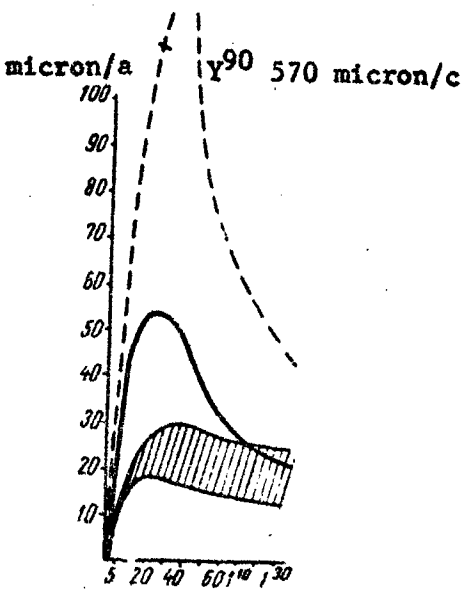


Fig. 1. Increase of permeability of the vessels of the ciliary tract three hours after the introduction of $Y^{90}$ into the hypophysis (rabbit No. 1463). Continuous line -- right eye; punctated line -- left eye. The limits of fluctuations of the removal of the dye in norm are shaded.

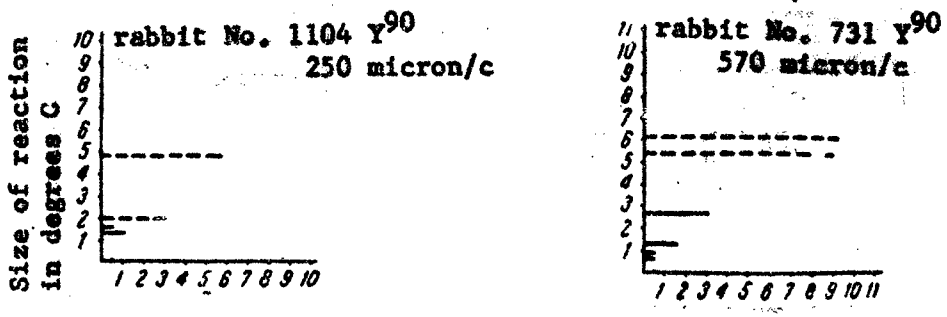


Fig. 2. Change of the size and duration of vascular reactions within three and four days following the introduction of $Y^{90}$ into the hypophysis. Continuous line -- before introduction; punctated line -- after introduction.

$Y^{90}$). After five to eight days, one observed the emergence of dilatory vascular reactions in response to the stimulation of the hypothalamic region, instead of normal constrictory ones. Despite the fact that we do not as yet possess the complete results of histological studies, the cited physiological data offer sufficient basis for such conclusion.

The calculation of the tissue doses for the hypophysis showed that during the periods when an inhibition of its function was observed the doses were equal to 25,000 - 38,000 rad. These doses correspond to the ones which are used in the clinic for the purpose of inhibiting the hypophyseal function.

Thus, as a result of the effect of $Y^{90}$ on the hypophysis, two categories of phenomena may develop: the inhibition of the hypophyseal function just described and the initial phase of stimulation. The clarification of the essence of the stimulation phase represents certain difficulty. As stated earlier, we separated the phenomena of true stimulation of the glandular tissue (increased permeability and an enhancement of vascular reactions). The origin of the other symptoms of the first phase (anisocoria, impaired thermoregulation, slower respiration, ECG changes) requires a special analysis. First of all, they can be regarded as the sequel of the stimulation of the centers of the hypothalamic region.

The stimulation phenomena can be caused by two mechanisms: the direct stimulating effect of radiation on the neural elements of the hypothalamus, also the hormonal influences of the hypophysis through the blood or by stimulation of the subthalamic region.

The probability of the direct stimulating effect of radiation on the hypothalamic region is confirmed by the data which demonstrated that tissue doses for the hypothalamus, with application of the Y90 activities, are sufficiently large and reach 1000 rad in some experiments (three hours after the operation).

Special experimental verification was required before this phenomena could be regarded as the result of stimulation.

With this in view, we turned to other objects. First of all, experiments were arranged with the application of Y90 to the superior cervical sympathetic node which represents the simplest neural apparatus with a monosynaptic transmission. This object is also convenient in that one can easily verify on it the phenomena of stimulation and the falling-out of functions. In order to judge the changes in the functional state of the superior cervical sympathetic

node, systematic observations were carried out on the size of the pupils, temperature fluctuations in the skin of the cochlea, recorddngs were made of the reactions of the pupils and the blood vessels of the ear to the stimulation of the sympathetic nerve. The same activities were instituted in these experiments as in the experiments with the hypophysis (150 micron/c up to 1.13 micron /c). The Y90 preparation was applied on the surface of the ganglion under the capsule. In none of these experiments could we note any symptoms of stimulation of the superior cervical sympathetic node. On the contrary, in some animals immediately following the isotope application in others starting on the third to fourth day, there were phenomena manifested characteristic of the paralysis of the sympathetic innervation. They manifested themselves in the contraction of the pupil on the operated side, falling-back of the eyeball, and pallor of the iris. During the same periods of time and up to the end of observation (12th to 14th day), stimulation of the cervical sympathetic nerve and the node itself induced no reactions in the pupil and the cutaneous blood vessels. On the basis of this, one can conclude that a complete cessation of the synaptic transfer in the ganglion took place at this time. In a number of cases the pupil, which had become contracted following the application of the Y90 preparation, dilated after seven to nine days and remained even more dilated than the pupil on the control side. This phenomenon may be connected with the phenomenon of enhanced sensitivity of denervated structures to adrenalin.

To clarify the problem of the possibility of a stimulating action of Y90 on the body of a neural cell, the application of the isotope on the Gasserian ganglion was employed (N. I. Arlashchenko). Yttrium was introduced through a trephination opening in the parietal bone and, after lifting the left temporal lobe of the brain, placed in a pocket on the anterior superior surface of the pyramid of the temporal bone The position of the preparation was controlled roentgenographically. Upon the use of a 850 micron/c dose, there was observed within two days after the operation and during the following three days a marked rise in the sensitivity of the cornea of the eye and the skin of the face on the operated side. A marked enhancement of the blinking reflex (four times more frequent) made it difficult to treat the obtained results as caused by a simple stimulation of the neuron body. Presumably, this effect represented the increase of stimulation of the reflex arc, trigeminus - facialis, and was connected with the radiation action on the centers. In favor of this idea

we may cite the results of experiments conducted in our laboratory by Tang Chih-ch'eng. The application of an ampule containing Sr90 on the spinal ganglion also elicited no effects of any antidromic stimulation of the afferent nerve which invariably appear in the trauma of a neuron. Tissue doses used by Tang Chih-ch'eng were approximately equal to our (600 rem). The application to the Gasserian ganglion of the Y90 preparation of 3.2 mc activity led within 24 hours to a complete loss of sensitivity of the cornea and of the skin on the face, and within two days -- to the development of keratitis on the operated side. These phenomena are analogous to those observed upon the separation of the trigeminal nerve.

In the experiment by Yu. G. Grigor'yev with the application of Y90 (2.5 mc) to the spinal cord (posterior columns) at the level of the seventh thoracic vertebra, one could note only the phenomena of falling-out, which manifested themselves in the loss of all types of sensitivity, development of paralysis, and the enhancement of vegetative reflexes of the spinal cord generally observed in its separation.

Thus, under the effect of Y90 one can observe in addition to the depression of the hypophyseal function, also brief manifestations of the increase of its secretory activity. These phenomena, under conditions of clinical application of yttrium, are undesirable; however, they are of a reversible character and do not lead to serious disturbances. It is important to stress the fact that under conditions of our experiments we observed no grave complications, in particular there was no impairment of vision despite the direct proximity to the chiasmus of the radioactive preparation placed in the hypophysis.

Among the side phenomena we described those caused by the effect on the hypothalamic region. According to the mechanism of their origin, these manifestations may be regarded as the result of its increased excitability. The basis for such an interpretation of the nature of the hypothalamic symptoms may serve the results of the experiments with the Y90 effect on the body of the neural cell (Gasserian ganglion), a simple monosynaptic apparatus, the transfers of neural stimulation (the superior cervical sympathetic ganglion), and such a complex neural mechanism as the spinal cord.

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